

# Evaluation of Plasma Fibrinogen Levels before and after Coronary Artery Bypass Graft Surgery and Its Association with the Need for Blood Products

## Abstract

**Background:** The present study investigated the plasma level of fibrinogen before and after removing the pump in coronary artery bypass graft (CABG) surgery and its relationship with the need for blood products. **Materials and Methods:** The present study was performed on 60 patients who were candidates for CABG surgery. The fibrinogen level of these patients was assessed and recorded before surgery and immediately after removing the pump. In addition, their hemoglobin level was recorded before the operation and 2 h after. In addition, the number and type of blood products transfusion were recorded intraoperatively and postoperatively and also at the intensive care unit. **Results:** Patients' fibrinogen level after removing the pump with the mean of  $130.53 \pm 122.01$  mg/dl decreased significantly compared to before surgery with the mean of mg/dl  $224.95 \pm 132.88$  mg/dl ( $P < 0.001$ ). In addition, the prognostic value of fibrinogen after removing the pump in determining the postoperative need of blood transfusion showed that the cut-off value of fibrinogen was  $< 196$  mg/dl with a sensitivity of 16.82% and specificity of 80%, but it was not statistically significant (area under the curve [95% confidence interval]: 0.519 [0.350–0.689];  $P = 0.825$ ). **Conclusion:** According to the results of the present study, due to significant changes in fibrinogen levels after removing the pump compared to preoperation, it seems that this factor can play an important role in prognosis of the need to postoperative blood transfusion, although the prognostic value and the critical point mentioned in our study was not significant and it is required to do further studies.

**Keywords:** Blood Transfusion, Coronary Artery Bypass Grafting, fibrinogen

## Introduction

Transfusion of blood and blood products is a significant portion of cardiac surgery.<sup>[1]</sup> Although 15%–20% of patients require cardiac surgery, more than 80% of blood products are consumed in this type of surgery.<sup>[2]</sup> In fact, the inherent feature of the cardiovascular surgery, especially when cardiopulmonary bypass (CPB) is involved in the occurrence of frequent bleedings during and after surgery, so that postoperative bleeding is a life-threatening complication in 5%–25% of cases. Therefore, the need for injecting blood products during and after surgery is inevitable.<sup>[3]</sup>

Therefore, as the prescription of blood products increases the risk of adverse outcomes, affects the patient outcome, and will also be associated with increased

medical costs,<sup>[4]</sup> it is preferable to avoid blood transfusion, and researchers aim at figuring out a way to minimize the need for blood products or to provide the required prognosis to prevent bleeding.<sup>[5,6]</sup>

Bleeding during the cardiac surgery may be influenced by patient-related factors and procedures, the use of anticoagulants, inflammation, consumption and dilution, clotting factors, and fibrinolysis associated with the use of CPB.<sup>[7]</sup> The substitution of major blood loss with red blood cells and colloid fluids leads to the development of plasma fibrinogen deficiency earlier than any other clotting factors,<sup>[8]</sup> which may, in turn, result in the excessive postoperative blood loss that requires transfusion of blood products.<sup>[9,10]</sup>

Therefore, fibrinogen seems to be the main risk factor for bleeding, modulates platelet aggregation, and determines

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**Received:** 31 January 2021

**Revised:** 15 April 2021

**Accepted:** 03 May 2021

**Published:** 30 March 2022

### Access this article online

**Website:** www.advbiores.net

**DOI:** 10.4103/abr.abr\_22\_21

### Quick Response Code:



**How to cite this article:** Honarmand A, Bagheri K, Hoghooghi A, Rezaei K. Evaluation of plasma fibrinogen levels before and after coronary artery bypass graft surgery and its association with the need for blood products. *Adv Biomed Res* 2022;11:25.

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plasma viscosity. Fibrinogen is an acute-phase reactant, is synthesized in the liver, increases in inflammatory states, and mediates the thrombogenic effect of other risk factors.<sup>[11]</sup> Elevated fibrinogen levels lead to the increased coagulation activity and are associated with increased cardiovascular disorders, atherosclerosis, peripheral vascular disease, and other thromboembolisms.<sup>[12]</sup>

However, little clinical information is available on the association of fibrinogen levels before and after CABG surgery with bleeding and the nontransfusion of blood products. Therefore, the present study aimed at investigating the association between plasma fibrinogen levels before and after CABG surgery with the need for blood products.

## Materials and Methods

The present study was a cross-sectional study. The study population was all patients that were candidates for open-heart surgery with the coronary artery bypass grafting (CABG) type in Chamran Hospital of Isfahan, Iran, during 2018–2019. The sample size was estimated to be 60 patients at the confidence level of 95%, test power of 80%, and the association of 0.35 between fibrinogen and the need for blood products. The sample was randomly selected from eligible patients meeting the inclusion criteria.

Inclusion criteria included being a candidate for CABG and over 18-year-old. If the patient had a prediagnosed coagulation disorder (a disorder that leads to the need for injecting anticoagulants, fresh frozen plasmas, platelets, or coagulation factors), they were not included in the study.

After obtaining the code of ethics from the Ethics Committee of Isfahan University of Medical Sciences (Code: IR.MUI.MED.REC.1399.171) and obtaining written consent from patients, demographic information of patients such as age, sex, weight, and comorbidities were recorded at the beginning of the study. In addition, fibrinogen and hemoglobin levels were assessed and recorded before the surgery. The use of inotropic, the duration of anesthesia, the time of CPB, and the number and type of blood products injected during surgery were also recorded. Moreover, the patients' fibrinogen level was measured immediately after off-pump CABG.

CABG was then performed for all patients. The number and type of injected blood products, the duration of anesthesia, the duration of intensive care unit (ICU), and the duration of ventilation were recorded after the surgery. Blood samples were taken from each patient 2 h after the surgery, and their hemoglobin level was measured again.

Finally, the data collected were entered into the Statistical Package for Social Sciences software (SPSS 23 for Windows; SPSS, Chicago, IL, USA). The data were presented as means  $\pm$  standard deviation or *n* (%). At

the level of inferential statistics, Mann–Whitney test was used to compare the mean of fibrinogen in transfused and nontransfused patients. Moreover, the Wilcoxon test was used to compare the mean of fibrinogen after off-pump CABG as compared to before the surgery. Finally, receiver operating characteristic (ROC) analysis was employed to achieve the prognostic value of the fibrinogen level in determining the need for blood products after the surgery and determining the area under the curve (AUC) indicators, sensitivity and specificity, positive predictive value (PPV), and negative predictive value (NPV). In all analyses, a significance level of  $<0.05$  was considered.

## Results

In the present study, out of 60 patients undergoing open-heart CABG surgery with a mean age of  $63.80 \pm 9.82$  years, 44 (73.3%) and 16 (26.7%) patients were male and female, respectively. Forty nine (81.7%) and 44 (73.3%) patients were in need of blood products during and after the surgery (in ICU), respectively. The number of blood product units required was 3–8. Other baseline and clinical characteristics of patients are presented in Tables 1 and 2.

Patients' fibrinogen level significantly decreased after off-pump CABG with a mean of  $130.53 \pm 122.01$  mg/dl as compared with before surgery with a mean of  $224.95 \pm 132.88$  mg/dl ( $P < 0.001$ ). However, the fibrinogen level was not significantly different before and after the intervention between transfused and nontransfused patients ( $P > 0.05$ ) [Figure 1].

Moreover, the need for blood products before and after the surgery did not differ significantly by patients' gender and age ( $P > 0.05$ ) [Table 3].

In addition, there was no significant difference in the decreased fibrinogen level after the off-pump CABG as compared to before the surgery by patients' gender, age, comorbidities, and smoking ( $P > 0.05$ ) [Table 4].

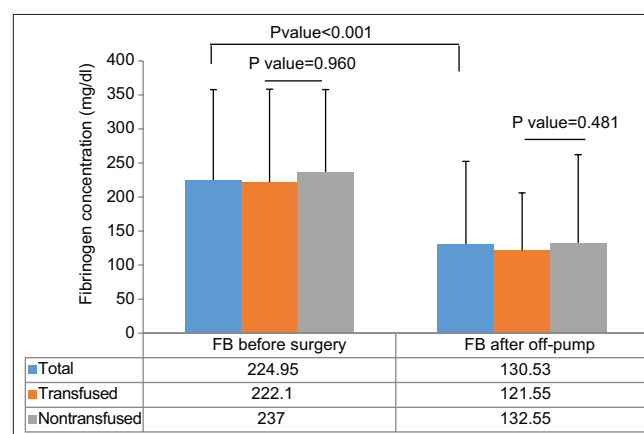


Figure 1: Comparison of the mean fibrinogen level based on the need to receive blood products

Finally, ROC analysis in identifying the prognostic value of fibrinogen after the off-pump CABG in determining the need of blood products after the surgery revealed the cut-off value of fibrinogen <196 mg/dl with the sensitivity of 16.82% and specificity of 80%, the PPV of 70%, and the NPV of 26%. However, it must be mentioned that the reported cut-off point was not statistically significant (AUC [95% confidence interval (CI)]: 0.519 [0.350–0.689];  $P = 0.825$ ) [Table 5].

**Table 1: Baseline and clinical characteristics of the study group**

Characteristics	Mean±SD or n (%)
Sex	
Male	44 (73.3)
Female	16 (26.7)
Age (year)	63.80±9.82
Weight (kg)	73.03±12.82
EF (%)	47.67±10.63
Comorbidities	
Diabetes	25 (41.7)
Hypertension	28 (46.7)
Hyperlipidemia	10 (16.7)
Other	1 (8.3)
Smoking	11 (18.3)
Opioid use	8 (13.3)
Used inotropes	
Dopamine	0
Dobutamine	7 (11.7)
Epinephrine	11 (18.3)
Norepinephrine	10 (16.7)

EF: Ejection fraction, SD: Standard deviation

**Table 2: Surgery-related variables of the study group**

Variables	Mean±SD or n (%)
HB before surgery (g/dl)	13.74±1.77
HB after surgery (g/dl)	9.51±1.13
Blood products during surgery	49 (81.7)
Type of blood products during surgery	
PC	1.23±0.87
FFP	0.72±1.89
PLT	0.68±1.72
Blood products after surgery	44 (73.3)
Type of blood products after surgery	
PC	1.52±1.35
FFP	0.63±1.49
PLT	0.35±1.27
Surgery duration (h)	3.96±0.68
Duration of anesthesia (h)	4.83±0.67
Time of CPB (min)	80.05±37.73
ICU duration (day)	3.44±1.30
Duration of ventilation (day)	12.23±7.96

HB: Hemoglobin, CPB: Cardiopulmonary bypass, SD: Standard deviation, PLT: Platelet, ICU: Intensive care unit, PC: Platelet concentrate, FFP: Fresh-frozen plasma

## Discussion

The results of the present study revealed that the transfusion rate of blood products (between 3 and 8 units) during and after the surgery was more than 70%. The study patients did not have anemia before the surgery, and their coagulation factors and fibrinogen levels were normal.

In this regard, Elmistekawy *et al.* reported that 67.6% and 13.3% of patients received more than 2 and 4 units of packed red blood cells (PRBC).<sup>[13]</sup> Another study indicated that 12% of patients received more than 3 units, and 48% of patients received between 1 and 3 units of PRBC.<sup>[14]</sup> Based on the results of previous studies, many factors such as the presence of anemia before surgery, aging, and decreased levels of hemoglobin, hematocrit, and

**Table 3: Frequency distribution of the need for blood products before and after surgery by patients' gender and age**

Factors	Blood products before surgery, n (%)	P	Blood products after surgery, n (%)	P
Sex				
Male	34 (69.4)	0.259	33 (75.0)	0.628
Female	15 (30.6)		11 (25.0)	
Age (years)				
<40	2 (4.1)	0.530	2 (4.6)	0.137
40-50	2 (4.1)		0	
50-60	13 (26.5)		14 (31.8)	
60-70	22 (44.9)		18 (40.9)	
>70	10 (20.4)		10 (22.7)	

**Table 4: Mean of decreased fibrinogen level after the off-pump coronary artery bypass graft as compared to before the surgery by patients' baseline and clinical characteristics**

Factors	Decreased fibrinogen	P
Sex		
Male	-128.82±133.58	0.327
Female	-166.31±118.52	
Age (years)		
<40	-260.00±188.09	0.955
40-50	-164.00±11.31	
50-60	-121.18±118.02	
60-70	-117.68±129.75	
>70	-176.54±148.46	
Comorbidities		
Diabetes (n=25)	-122.52±139.64	0.416
Hypertension (n=28)	-128.78±113.93	
Hyperlipidemia (n=10)	-171.30±88.22	
Other (n=5)	-25.6±92.34	
Smoking		
Yes	-86.73±82.12	0.054
No	-150.51±136.21	

**Table 5: The prognostic value of fibrinogen after off-pump in determining the need of blood products**

Parameters of ROC analysis	Fibrinogen after off-pump (mg/dl), % (95% CI)
AUC	0.519 (0.350-0.689)
<i>P</i>	0.825
Cut-off point	<196
Sensitivity	16.82 (4.55-38.64)
Specificity	80.00 (54.40-94.00)
PPV	70.00 (34.80-93.31)
NPV	26.00 (14.64-40.36)

ROC: Receiver operating characteristic, AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

fibrinogen were significantly associated with the increased bleeding and the increased need for blood products.<sup>[15-17]</sup> However, what has recently received researchers' due attention is the evaluation of patients' blood factors as many of the above-mentioned factors are unmanageable. Therefore, it may be conceivable to prevent bleeding and the need for the transfusion of blood products by controlling the level of blood factors, especially fibrinogen levels before or during surgery.

In the present study, the patients' fibrinogen level decreased after the pump-off as compared to before surgery ( $P < 0.001$ ). However, its mean in transfused patients was slightly lower and nonsignificant than nontransfused patients ( $P > 0.05$ ). In addition, this study examined the association of both the patients' need for blood products and the reduction of fibrinogen levels with factors such as age and sex and found no significant association between the mentioned factors and the need for blood products before or after the surgery and decreased fibrinogen levels.

Contrary to the findings of the present study, some previous studies revealed that aging and sex (female) as independent risk factors have been associated with the increased blood transfusion after cardiac surgery.<sup>[18]</sup> However, in line with the findings of the present study, Karlsson *et al.* did not find a significant association between age and blood transfusion.<sup>[19]</sup> More bleeding and more transfusion of blood product in women can be attributed to the lower hemoglobin levels and the lower total blood volume. However, the mentioned association has not been proven in all studies.

Fibrinogen is the major plasma protein for fibrin configurations and homeostasis.<sup>[20]</sup> Fibrinolysis has been shown to be responsible for 25%–45% of significant bleedings after bypass.<sup>[21]</sup> That is why the level of fibrinogen before surgery, after surgery, or during the pump-off CABG in the prognosis of bleeding or the need for blood products has received many surgeons' due attention so that the risks of transferring blood products to patients can be avoided by controlling the fibrinogen level.

According to previous studies, plasma fibrinogen levels below 200 mg/dl may be associated with an increased risk of postoperative bleeding after cardiac surgery. CPB during surgery causes a significant drop in plasma fibrinogen levels, which in turn will lead to the excessive postoperative bleeding.<sup>[22,23]</sup>

In the present study, the cut-off point of fibrinogen level after the pump-off CABG in the prognosis of bleeding 2 h after the surgery was <196 mg/dl with the sensitivity and specificity of 16.50% and 80%, respectively.

In a large sample size study, Karkouti *et al.* indicated that the probability of a large volume transfusion at the fibrinogen level of <200 mg/dl increased with a sensitivity of 50% and specificity of 60% such that 42% of patients had less than this fibrinogen level and 18.9% of patients with the mentioned fibrinogen level had a large volume transfusion as compared to patients with the fibrinogen level of more than 200 mg/dl.<sup>[24]</sup>

Alagha *et al.* also revealed that preoperative plasma fibrinogen concentration of <3.1 g/l was significantly associated with an increased risk of excessive bleeding in patients undergoing on-pump CABG.<sup>[21]</sup> Although this study did not examine the association between fibrinogen levels before surgery and transfusion of intraoperative and postoperative blood products, many underlying factors may affect bleeding surgery or the need for postoperative blood products. Therefore, the consideration of fibrinogen levels before surgery may not be very reliable.

The current study also paid due attention to the fibrinogen level after pump-off CABG in the prognosis of bleeding after surgery. Although the reported cut-off point was not statistically significant, its PPV was 70% and accurately warned of the increased likelihood of the transfusion blood products in study patients.

Cut-off values ranging from 1.44 to 2.85 g/l have been established in a number of studies addressing the best combination of specificity and sensitivity to describe the postoperative fibrinogen level linked to bleeding.<sup>[25-27]</sup> In this regard, the cut-off value of 2.2 g/l, sensitivity of 67%, and specificity of 57% have been reported by Kindo *et al.* However, the evaluation of a PPV can be considered as a more acceptable estimation of trigger values the supplementation of fibrinogen in case of excessive bleeding.<sup>[24,10]</sup> Ranucci *et al.* reported that the fibrinogen level of 1.15 g/l yielded a PPV of 50%.<sup>[28]</sup>

Finally, it is important to note that the assessment of fibrinogen levels before surgery, after the pump-off CABG, or after surgery in the prognosis of the need for blood products by consideration of the gender or age of patients could be significant and interesting; however, the present study did not obtain valuable results because of the small sample size. In addition, as previous studies have examined the association between fibrinogen levels and bleeding

during and after surgery, this study examined the need for blood products, which is directly related to bleeding, with a different perspective that can be regarded as one of the strengths of this study because calculating the volume of bleeding, especially during surgery can be difficult and erroneous and may not be accurate enough. Finally, it is suggested that future studies with larger sample sizes assess the level of fibrinogen after the pump-off CABG with bleeding or the need for blood products after surgery so that the results can be more confidently generalized to the target population.

## Conclusion

According to the results of the present study, the fibrinogen level after the pump-off CABG as compared to before the surgery significantly reduced. In addition, the fibrinogen cut-off point in the prognosis of the need to receive blood products after the surgery was found to be less than 196 mg/dl with a high PPV and specificity though it was not statistically significant.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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